PROCESS FOR THE INDUSTRIAL SYNTHESIS OF STRONTIUM RANELATE AND ITS HYDRATES

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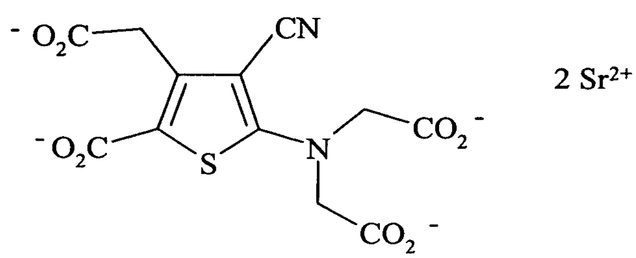
Title of the invention :

The present invention relates to a process for the industrial synthesis of strontium ranelate of formula (I) :



(I)

(the distrontium salt of 5-[bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid), and its hydrates.

Background of the Invention :

Strontium ranelate has very valuable pharmacological and therapeutic properties, especially pronounced anti-osteoporotic properties, making this compound useful in the treatment of bone diseases.

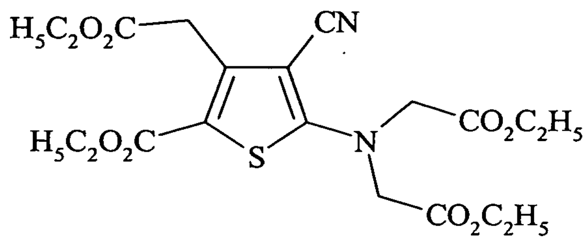
Strontium ranelate, its preparation and its therapeutic use have been described in the European Patent Specification EP 0 415 850.

However, industrial production of a compound such as strontium ranelate requires detailed study of all the reaction steps and of the selection of starting materials, reagents and solvents in order to obtain optimum yields.

The Applicant has developed a synthesis process for strontium ranelate of formula (I) in which such conditions have been combined, resulting in the use of a whole group of especially valuable methods and procedures.

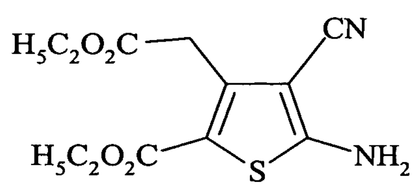
Description of the Prior Art :

The Patent Specification EP 0 415 850 describes the synthesis of strontium ranelate starting from the ethyl tetraester of formula (IIa) :



(IIa),

which is itself obtainable starting from the ethyl diester of formula (IIIa) :



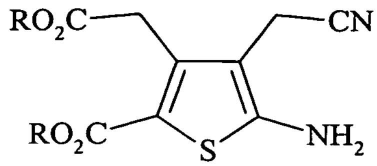
(IIIa).

Synthesis of the intermediate of formula (IIIa) has been described in the publication Bull. Soc. Chim. France 1975, pp. 1786-1792 and in the publication J. Chem. Tech. Biotechnol. 1990, 47, pp. 39-46, by reaction between diethyl 3-oxoglutarate, malononitrile and sulphur in ethanol, in the presence of morpholine or diethylamine.

That process has the advantage of using readily accessible starting materials and of being simple to put into practice; however, when transferred to the scale of several hundred kilograms, it does not allow the compound of formula (IIIa) to be obtained in a yield greater than 70 %.

Detailed description of the Invention :

In order to synthesise strontium ranelate of formula (I) industrially, the Applicant has developed an effective industrial synthesis process allowing the intermediate of formula (III) :

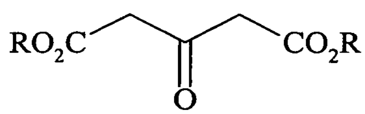


(III),

wherein R represents a linear or branched $(C_1\text{-}C_6)$alkyl group,

to be obtained with a purity greater than 97 % and in a yield of 77 %, which is reproducible on an industrial scale.

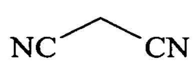
More specifically, the industrial synthesis of the diester of formula (III) which has been developed by the Applicant for the industrial synthesis of strontium ranelate of formula (I) uses, as starting material, the compound of formula (IV) :



(IV),

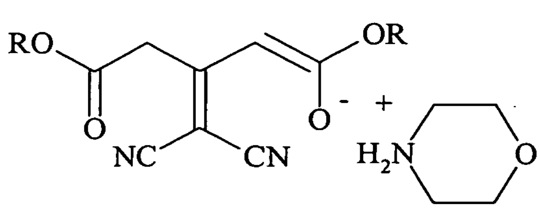
wherein R is as defined hereinbefore,

which is reacted with malononitrile of formula (V) :



(V)

in methanol,
in the presence of morpholine in an amount greater than 0.95 mol per mol of compound of formula (IV),
to yield the compound of formula (VI) :



(VI),

wherein R is as defined hereinbefore,
which is then reacted with sulphur in an amount greater than 0.95 mol per mol of compound of formula (IV);
the reaction mixture is then heated at reflux;
and the compound of formula (III) thereby obtained is isolated by precipitation in the presence of water, followed by filtration.

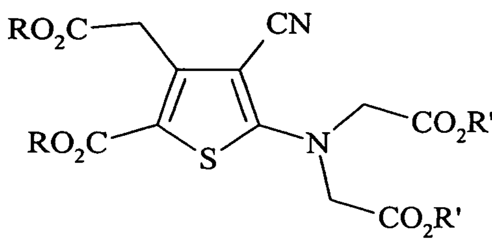
The process, accordingly improved by the use of these very specific conditions, and especially by the intermediate formation of the compound of formula (VI), which can, if desired, be isolated, allows the compound of formula (III) to be obtained with excellent purity and in a yield of at least 77 % which is reproducible on the scale of several hundred kilograms, which represents a major gain in yield in view of the large tonnages of strontium ranelate produced.

The amount of methanol is preferably from 1 to 3 ml per gram of compound of formula (IV).

The temperature of reaction between the compounds of formulae (IV) and (V) is preferably less than 50°C.

The reaction time at reflux after addition of the sulphur is preferably from 1 hour 30 minutes to 3 hours.

The second step in the process for the industrial synthesis of strontium ranelate of formula (I) developed by the Applicant comprises converting the compound of formula (III) into the compound of formula (II) :



(II),

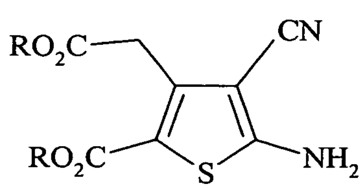
wherein R is as defined hereinbefore and R' represents a linear or branched (C_1-C_6)alkyl group.

The journal Bull. Soc. Chim. France 1975, pp. 1786-1792, describes obtaining the compound of formula (IIa), a particular case of the compounds of formula (II) wherein R = R' = ethyl), by reacting 5-amino-3-(carboxymethyl)-4-cyano-2-thiophenecarboxylic acid with ethyl bromoacetate, in the presence of potassium carbonate, followed by isolation in a highly dilute aqueous-organic medium.

However, the low yield of that reaction (65 %), the large amount of aqueous saline waste generated by that reaction and, above all, the very long reaction time (5 days) have completely precluded the use of that reaction on an industrial scale.

In order to synthesise strontium ranelate of formula (I) industrially, the Applicant has developed a simple industrial synthesis process which allows the compound of formula (II) to be obtained in a very good yield, with a considerably shorter reaction time and excellent purity and in which the aqueous saline waste is completely avoided.

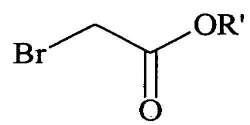
More specifically, the industrial synthesis of the tetraester of formula (II) which has been developed by the Applicant for the synthesis of strontium ranelate of formula (I) uses, as starting material, the compound of formula (III) :



(III),

wherein R represents a linear or branched $(C_1\text{-}C_6)$alkyl group,

which is reacted with a compound of formula (VII) :



(VII),

wherein R' represents a linear or branched $(C_1\text{-}C_6)$alkyl group, in the presence of a catalytic amount of a $C_8\text{-}C_{10}$-type quaternary ammonium compound, and in the presence of potassium carbonate, at the reflux of an organic solvent; the reaction mixture is subsequently filtered; the mixture is then concentrated by distillation; a co-solvent is then added, and the reaction mixture is cooled and filtered to yield, after drying of the powder thereby obtained, the compound of formula (II).

A $C_8\text{-}C_{10}$-type quaternary ammonium compound is understood to be a compound of formula (A) or a mixture of compounds of formula (A) :

$$R_1 R_2 R_3 R_4\text{-}N^{+} {}^{-}X \qquad \text{(A)}$$

wherein R_1 represents a $(C_1\text{-}C_6)$alkyl group, R_2, R_3 and R_4, which are the same or different, each represent a $(C_8\text{-}C_{10})$alkyl group, and X represents a halogen atom.

$C_8\text{-}C_{10}$-type quaternary ammonium compounds to which preference is given are the catalysts Adogen 464® and Aliquat 336®.

Surprisingly, only the use of a $C_8\text{-}C_{10}$-type quaternary ammonium compound allows the compound of formula (I) to be obtained both with a greatly reduced reaction time and with very good selectivity, in contrast to other types of quaternary ammonium compounds, as the following Table shows :

Catalyst	Duration of reaction	Content of reaction mixture
Tetrabutylammonium hydrogen sulphate (TBAHS)	12 hours	92 %
N,N-bis(2-hydroxyethyl)-N-methyl 1-dodecanaminium bromide	18 hours	82 %
Adogen 464®	5 hours	96 %
Aliquat 336®	4 hours	95 %

Furthermore, the somewhat simplified isolation (the precipitation step followed by filtration has been replaced by simple filtration of the reaction mixture) allows, by virtue of the particular conditions developed, the compound of formula (II) to be obtained not only in a very good yield (89 %) but also with excellent purity (greater than 98 %), whilst avoiding the burden on the environment that the aqueous saline waste represented.

- The amount of potassium carbonate is preferably from 2 to 3 mol per mol of compound of formula (III).

- The amount of compound of formula (VII) is preferably from 2 to 3 mol per mol of compound of formula (III).

- The initial volume of organic solvent is preferably from 6 to 12 ml per gram of compound of formula (III).

- The organic solvents that are preferred for the reaction are acetone and acetonitrile.

- The co-solvent that is preferred for isolation is methanol.

The third and final step in the process for the industrial synthesis of strontium ranelate of formula (I) developed by the Applicant comprises converting the tetraester of formula (II) into the distrontium salt of the corresponding tetraacid.

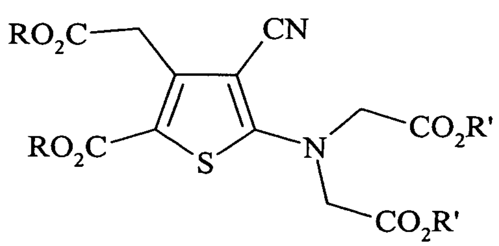
The Patent Specification EP 0 415 850 describes three methods for that conversion. The third of the methods described, which comprises heating the compound of formula (IIa), a particular case of the compounds of formula (II), in an aqueous alcoholic medium, with strontium hydroxide, and then distilling off the ethanol and isolating the compound of formula (I) by precipitation, has the advantage of being extremely simple to perform.

However, whilst operating under the conditions described for that third method, the Applicant has obtained strontium ranelate only in a yield of 80 % and with a purity of 87 %.

In view of the fact that strontium ranelate is insoluble in most solvents, its subsequent purification is extremely laborious. Such a method has therefore been incompatible with use of the strontium ranelate as a pharmaceutical active ingredient, which requires a purity greater than or equal to 98 %.

The Applicant has developed an industrial synthesis process allowing strontium ranelate to be obtained not only with excellent chemical purity so that it does not require further treatment before being used as a pharmaceutical active ingredient but also in an excellent yield.

More specifically, the final step in the process for the industrial synthesis of strontium ranelate of formula (I) developed by the Applicant uses the compound of formula (II) :



(II),

wherein R and R', which are the same or different, each represent a linear or branched (C_1-C_6)alkyl group, R preferably representing a methyl group and R' preferably representing a methyl or ethyl group,

which is reacted with strontium hydroxide in an amount greater than or equal to 2 mol per mol of compound of formula (II),
at the reflux of water,
for at least 5 hours;
the precipitate obtained is then filtered off whilst hot;
the cake obtained is washed with boiling water
to yield, after drying of the powder thereby obtained, the compound of formula (I) and its hydrates.

- Surprisingly, replacement of the ethanol/water mixture by water alone dramatically improves not only the purity of the strontium ranelate obtained but also the yield.

- Moreover, dispensing with the ethanol distillation step further simplifies the process.

The amount of water in the reaction mixture is preferably greater than or equal to 8 ml per gram of compound of formula (II).

The amount of strontium hydroxide is preferably from 2 to 2.5 mol per mol of compound of formula (II).

The Examples hereinbelow illustrate the invention but do not limit it in any way.

Examples 1A and 1B illustrate the first step in the Applicant's process for the industrial synthesis of strontium ranelate; Examples 2A, 2B, 2C and 2D illustrate the second step in that process; finally, Example 3 illustrates the third and last step in that process.

<u>EXAMPLE 1A</u> : Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophene-carboxylate

Introduce into a reactor 400 kg of dimethyl 3-oxoglutarate, 158 kg of malononitrile and 560 litres of methanol and then, whilst maintaining the temperature of the reaction mixture below 40°C, 199.6 kg of morpholine.

Then introduce 73.6 kg of sulphur and subsequently bring the mixture to reflux.

After reacting for 2 hours, stop refluxing and add water until precipitation occurs. Filter off the precipitate obtained, wash it and dry it.

Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is thereby obtained in a yield of 77 % and with a chemical purity of 98 %.

<u>EXAMPLE 1B</u> : Methyl 5-amino-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophene-carboxylate

Introduce into a reactor 400 kg of dimethyl 3-oxoglutarate, 158 kg of malononitrile and 560 litres of methanol and then, whilst maintaining the temperature of the reaction mixture below 40°C, 199.6 kg of morpholine.

The compound of formula (VI) thereby obtained, or the addition salt of methyl 3-(dicyanomethylene)-5-hydroxy-5-methoxy-4-pentenoate with morpholine, is isolated by filtration after cooling of the mixture and is then reacted with 73.6 kg of sulphur in methanol.

The mixture is then brought to reflux.

After reacting for 2 hours, stop refluxing and add water until precipitation occurs. Filter off the precipitate obtained, wash it and dry it.

EXAMPLE 2A : Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate

Introduce into a reactor 400 kg of 5-amino-3-(carboxymethyl)-4-cyano-2-thiophene-carboxylic acid, 478 kg of potassium carbonate, 2810 litres of acetone, 16 kg of Adogen 464® and 529.6 kg of methyl bromoacetate.

Bring the temperature to 60°C. After refluxing for 5 hours, cool the reaction mixture and then filter it. Concentrate the filtrate obtained.

Add methanol; cool and filter the suspension obtained, and then dry the powder.

Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is thereby obtained in a yield greater than 85 % and with a chemical purity greater than 98 %.

EXAMPLE 2B : Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate

Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is obtained in the same manner as Example 1, but replacing Adogen 464® by Aliquat 336®.

EXAMPLE 2C : Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate

Methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is obtained in the same manner as Example 1, but replacing the acetone by acetonitrile.

EXAMPLE 2D : Methyl 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate

Methyl 5-[bis(2-ethoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate is obtained in the same manner as Example 1, but replacing the 529.6 kg of methyl bromoacetate by 578.1 kg of ethyl bromoacetate.

EXAMPLE 3 : 5-[Bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid distrontium salt octahydrate

Introduce into a reactor 770 kg of strontium hydroxide and 5,500 litres of water and then 550 kg of methyl 5-[bis(2-methoxy-2-oxoethyl)amino]-4-cyano-3-(2-methoxy-2-oxoethyl)-2-thiophenecarboxylate. Heat to reflux and continue refluxing for a minimum of 5 hours; then filter the reaction mixture whilst hot, wash the cake with boiling water and dry the powder obtained.

5-[Bis(carboxymethyl)amino]-3-carboxymethyl-4-cyano-2-thiophenecarboxylic acid distrontium salt octahydrate is thereby obtained in a yield of 96 % and with a chemical purity of 98 %.